A practical guide to arylbiguanides — Synthesis and structural characterization[1]

Olivier LeBel, Thierry Maris, Hugues Duval, and James D. Wuest

Abstract: Monohydrochloride salts of diverse 1-arylbiguanides and 1,5-diarylbiguanides were synthesized by the reaction of anilinium chlorides with dicyandiamide or sodium dicyanamide, and the biguanidinium chlorides were converted into the corresponding biguanides by deprotonation with methanolic $NaOCH_3$. The resulting biguanides and their salts were fully characterized by spectroscopic methods, and the structures of representative compounds were determined by X-ray crystallography.

Key words: biguanide, biguanidinium, synthesis, structure, hydrogen bonds, noncovalent interactions, supramolecular chemistry.

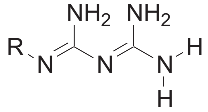
Résumé : On a effectué la synthèse de monochlorhydrates de divers 1-arylbiguanides et de 1,5-diarylbiguanides en faisant réagir des chlorures d'anilinium avec du dicyandiamide ou du dicyanamidure de sodium. Les chlorures de biguanidium ont été transformés en biguanides correspondants par déprotonation avec une solution méthanolique de $NaOCH_3$. Les biguanides correspondants et leurs sels ont été complètement caractérisés par des méthodes spectroscopiques et les structures de composés représentatifs ont été déterminées par diffraction des rayons X.

Mots clés : biguanide, biguanidinium, synthèse, structure, liaisons hydrogène, interactions non covalentes, chimie supramoléculaire.

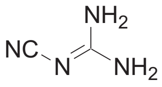
[Traduit par la Rédaction]

Introduction

The general class of compounds called biguanides has been known for more than 100 years (1–3). An early method for preparing salts of biguanide itself (**1**) was reported in 1892 by Bamberger and Dieckmann (4), who heated dicyandiamide (**2**) with ammonium chloride and then isolated the product by forming an intermediate biguanide-copper (II) complex.[4] Since then, biguanides have proven to be broadly useful. In medicine, they have important applications as antiseptics (5), antimalarials (6, 7), serotoninergic antagonists (8), antitumoral agents (9), and hypoglycemic agents (10, 11). In addition, the ability of biguanides to chelate metals has been widely used in coordination chemistry since the initial observations of Bamberger and Dieckmann (1, 3). Moreover, biguanides are strong bases (12, 13), and they are also valuable precursors for synthesizing a wide range of heterocyclic compounds (2, 14). Of special interest among the heterocyclic derivatives of biguanides are aminotriazines, which are themselves an extremely useful family of compounds. For example, they are widely used in supramolecular chemistry because they incorporate a characteristic pattern of multiple sites that can donate or accept hydrogen bonds, thereby directing molecular recognition and association. In particular, recent applications of aminotriazines in crystal engineering have highlighted their ability to direct crystallization by self-associating according to reliable hydrogen-bonding motifs (15, 16).



1 (R = H)
3 (R = Ph)
13 (R = CH_2CH_2Ph)



2

Our motivation for studying substituted biguanides stems from their potential as precursors of novel aminotriazines and from the possibility that the multiple sites of hydrogen bonding in the biguanides themselves may make them valuable components in supramolecular assembly. Unfortunately, despite the demonstrated utility of biguanides and the likelihood of new applications, few detailed syntheses and structural characterizations have been previously reported, and information about 1-aryl- and 1,5-diarylbiguanides remains

Received 23 December 2004. Published on the NRC Research Press Web site at http://canjchem.nrc.ca on 11 June 2005.

Dedicated with respect and affection to Professor Howard Alper for his friendship, wise counsel, pioneering research, and tireless service to Canadian chemistry.

O. LeBel,[2] T. Maris, H. Duval, and J.D. Wuest.[3]
Département de Chimie, Université de Montréal, Montréal, QC H3C 3J7, Canada.

[1] This article is part of a Special Issue dedicated to Professor Howard Alper.

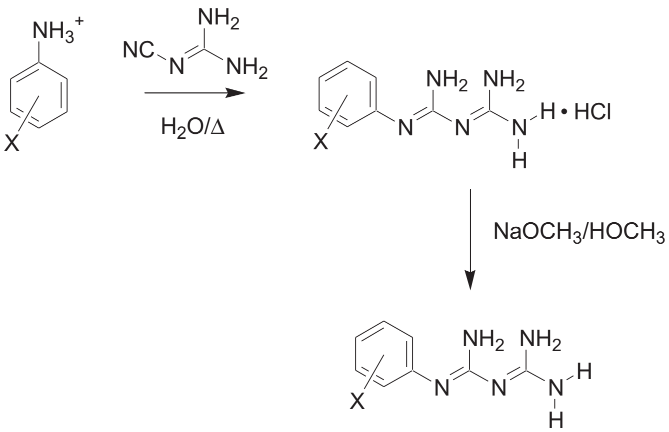
[2] Fellow of the Ministère de l'Éducation du Québec (2002–2004).

[3] Corresponding author (e-mail: james.d.wuest@umontreal.ca).

[4] For the sake of simplicity, biguanides, dicyandiamide, and related compounds are normally represented in this paper as single tautomers.

doi: 10.1139/V05-093

Scheme 1.

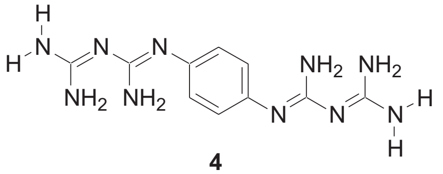


particularly sparse (17–38). To supply missing data and give other researchers a practical guide to the field, we report here the synthesis and full characterization of a series of arylbiguanides, along with crystal structures of representative compounds.

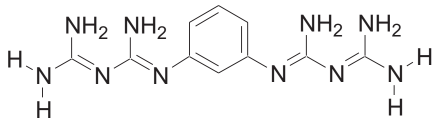
Results and discussion

Synthesis of 1-arylbiguanides

To synthesize monosubstituted 1-arylbiguanides, we used a modification of a procedure reported in a 1946 patent by Curd and Rose (23), who heated anilinium salts with dicyandiamide in water (Scheme 1). The hydrochloride salts of the arylbiguanides generally crystallize from the reaction mixture in good yield and in high purity, and they can be deprotonated with methanolic sodium methoxide in nearly quantitative yield. Detailed procedures for making 1-phenylbiguanide (**3**) and its hydrochloride salt by these methods are provided in the Experimental section, and other aryl-substituted derivatives can be made in the same way. When 1,4- or 1,3-phenylenediamine dihydrochloride reacted under these conditions with 2 equiv. of dicyandiamide, the corresponding bis(biguanide) (**4** or **5**) was obtained after deprotonation (39), whereas 1,2-phenylenediamine dihydrochloride gave 2-guanidinobenzimidazole (40).

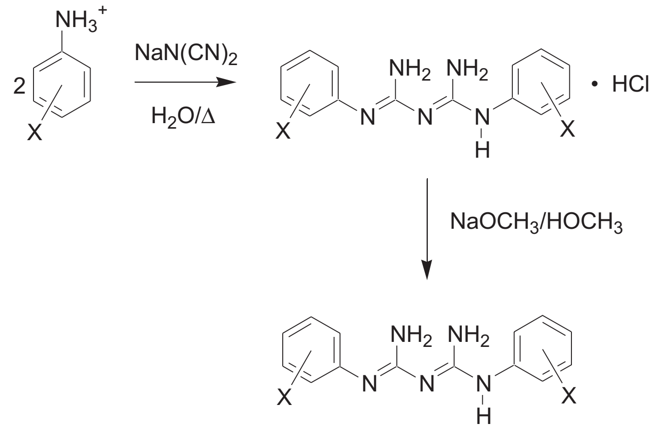


4



5

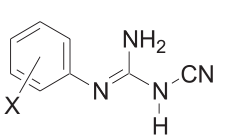
Scheme 2.



6a (X = X' = H)
6b (X = X' = 2-CH_3)
6c (X = X' = 3-CH_3)
6d (X = X' = 4-CH_3)
6e (X = X' = 4-OCH_3)
6f (X = X' = 4-CN)
6g (X = X' = 2-Br)
6h (X = X' = 4-Br)
6i (X = X' = 3,5-CH_3)
6j (X = X' = 2,4,6-CH_3)

Synthesis of 1,5-diarylbiguanides

1,5-Diarylbiguanides **6a**–**6j** could be synthesized in good yield by a one-pot procedure based on a method reported by Neelakantan (22), in which 2 equiv. of an anilinium chloride are added to sodium dicyanamide in boiling water (Scheme 2). In the case of anilines with low solubility in water, the reaction can be performed in ethanol or in water–ethanol mixtures. Of all anilines tested, only 4-nitroaniline failed to give the desired product, presumably because its basicity and nucleophilicity are too low. A monosubstituted aryldicyandiamide (**7**) typically precipitated at an initial stage of each reaction, but the intermediate was eventually converted into the desired diarylbiguanide as its hydrochloride salt. It is possible to isolate the intermediate monoaryldicyandiamides and use them to synthesize unsymmetric 1,5-diarylbiguanides. For example, phenyldicyandiamide (**7**, X = H) was obtained in this way in 87% yield.



7

After the reaction of 2 equiv. of an anilinium chloride with sodium dicyanamide, the crude product typically consisted of the desired diarylbiguanide hydrochloride along with small amounts of the intermediate monoaryldicyandiamide. This impurity could be removed by dissolving the product in a small volume of DMF and then precipitating the biguanide hydrochloride by the addition of toluene. The resulting product normally required no further purification, but it could be recrystallized from hot water. Pure samples of the corresponding free base could be obtained in nearly quantitative yield by treating the salt with methanolic sodium hydroxide.

Spectroscopic characterization of arylbiguanides

Arylbiguanides typically have poor solubility in organic solvents and water, and DMSO-d_6 proved to be best suited for obtaining NMR spectra of most of the compounds synthesized. The -NH and -NH_2 protons in these compounds generally show broad, poorly resolved peaks in the range δ 5–9. However, the corresponding monohydrochloride salts produce spectra in which the -NH and -NH_2 signals are better resolved and easier to identify. In the salts, the aryl -NH protons tend to give rise to a singlet near δ 9 to 10, and -NH_2 groups yield signals in the range δ 7 to 8.

To assess the possible importance of slow interconversion of tautomers or slow rotations around C—N bonds, ^{1}H NMR spectra of 1,5-diphenylbiguanide (**6a**) and its hydrochloride salt were recorded in DMSO-d_6 at temperatures ranging from 298 to 378 K (see Supplementary material).[5] The spectra of both compounds are indeed temperature-dependent and become better resolved at higher temperatures, possibly because rotations or tautomeric interconversions are accelerated. Partial decomposition was noted in spectra of the free base recorded at higher temperatures.

In general, the hydrochloride salts of both 1-arylbiguanides and 1,5-diarylbiguanides gave well-resolved ^{13}C NMR spectra in DMSO-d_6 at 298 K. The biguanide carbons have characteristic chemical shifts in the range δ 155–165. In contrast, the ^{13}C NMR spectra of the corresponding free bases are less easy to analyze, and broad signals are often observed for the biguanide carbons.

FT-IR spectra of arylbiguanides and their monohydrochloride salts in KBr both show multiple strong broad bands in the range 2900–3300 cm^{-1}. In addition, the free bases exhibit a pair of sharper but weaker bands near 3440 and 3350 cm^{-1}, presumably owing to -NH_2 groups. In both the free bases and salts, strong C=N stretching bands normally appear near 1640–1610 cm^{-1}.

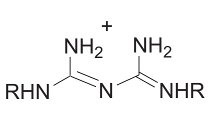
FAB and MAB mass spectra proved to be useful for characterizing arylbiguanides, and $[M + H]^+$ is typically the peak of highest intensity. Diagnostic fragments usually include $[M + H – NH_3]^+$, $[M + H – ArNH_2]^+$, $[M + H – ArNHCN]^+$, and $[M + H – ArN{=}C(NH_2)_2]^+$.

Crystal structures of 1,5-diphenylbiguanide (6a) and its monohydrochloride salt

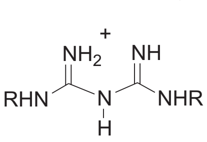
Few structures of simple biguanidinium salts or biguanides have been reported (25–38), and in none of these cases have aryl groups been present at positions 1 and 5. As a result, we elected to determine the structures of 1,5-diphenylbiguanide (**6a**) and its monohydrochloride salt. The salt crystallized from hot water in the monoclinic space group $P2_1/n$ (Table 1).[5] The structure was determined by X-ray diffraction, and views of a single biguanidinium cation are shown in Fig. 1. The narrow range of guanidinium C—N bond lengths (1.343–1.394 Å) provides evidence of extensive delocalization, although the structure is not fully symmetric. It is noteworthy that the cation can be represented by localized structure **8** and its resonance hybrids, whereas alternatives in which the central nitrogen atom is protonated (**9**) or an intramolecular hydrogen bond is formed (**10**) are not favored in the solid state. Similar observations have been made in all previous structural studies of biguanidinium cations (25, 26, 28–34, 36–38), so protonation of biguanides to give struc-

Table 1. Crystallographic data for the hydrochloride salt of 1,5-diphenylbiguanide (**6a**·HCl) and for 1,5-diphenylbiguanide (**6a**).

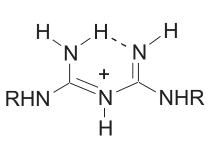
Compound	**6a**·HCl	**6a**
T (K)	293	100
λ (Å)	1.541 78 (CuKα)	1.541 78 (CuKα)
Formula	$C_{14}H_{16}ClN_5$	$C_{14}H_{15}N_5$
Fw	289.77	253.31
F(000)	608	536
Crystal system	Monoclinic	Monoclinic
Z	4	4
d (g cm^{-3})	1.146	1.308
μ (mm^{-1})	1.994	0.663
Space group	$P2_1/n$	Pc
a (Å)	9.627(5)	9.031 7(3)
b (Å)	4.975 1(5)	6.394 5(2)
c (Å)	35.253 3(5)	22.587 4(8)
α (°)	90	90
β (°)	95.79(2)°	99.588(2)°
γ (°)	90°	90°
Volume (Å^3)	1679.9(9)	1286.27(7)
θ max (°)	66.4	71.9
h, k, l max	11, 5, 41	11, 7, 27
Unique	2854	2530
Observed ($I > 2\sigma(I)$)	2025	1570
R_1	0.058 7	0.067 3
$wR2$	0.179 0	0.152 5
$R1$ (all data)	0.067 6	0.074 5
$wR2$ (all data)	0.187 4	0.155 1
Diff. peak and hole (e/Å^3)	0.325/–0.273	0.321/–0.327
GoF	1.069	1.024



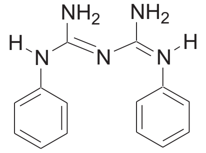
8



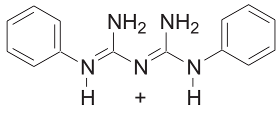
9



10



11



12

---

[5] Supplementary data for this article are available on the Web site or may be purchased from the Depository of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Ottawa, ON K1A 0S2, Canada. DUD 3662. For more information on obtaining material refer to http://cisti-icist.nrc-cnrc.gc.ca/irm/unpub_e.shtml. CCDC 258751–258752 contain the crystallographic data for this manuscript. These data can be obtained, free of charge, via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax +44 1223 336033; or deposit@ccdc.cam.ac.uk).

Fig. 1. Two views of the structure of individual biguanidinium cations in the crystals of the hydrochloride salt of 1,5-diphenylbiguanide (**6a**·HCl) grown from water. Hydrogen atoms appear in white, carbon atoms in gray, and nitrogen atoms in black. The upper view provides C—N bond lengths, and the lower view shows the intramolecular C-H···π interaction (broken line) present in the biguanidinium ion. All bond lengths are in Å (with standard deviations provided in the Supplementary material),[5] and the shortest C—C distance between the phenyl rings is used to define the aromatic interaction.

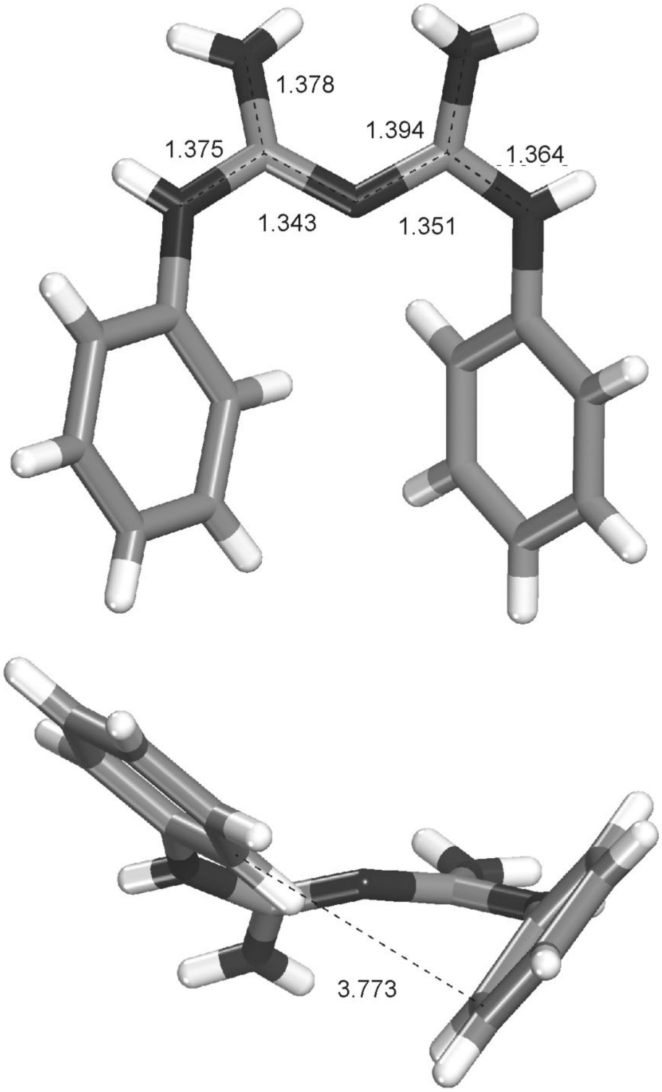
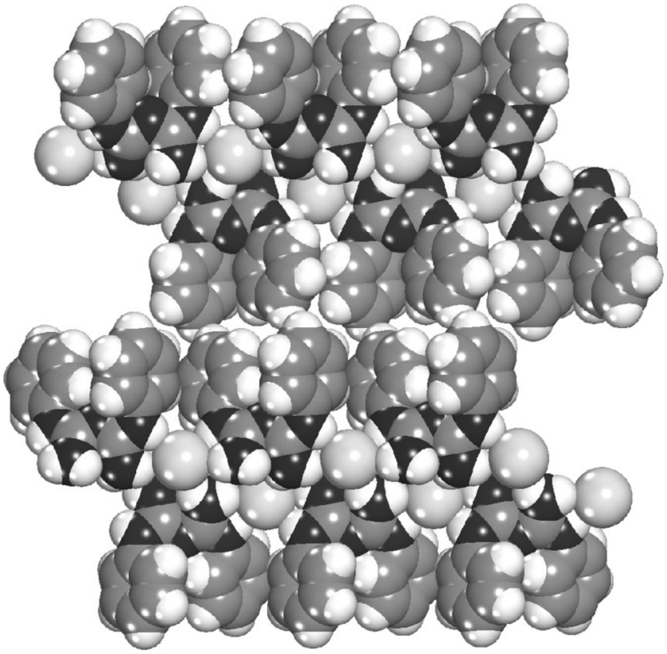


Fig. 2. View along the *b* axis of the structure of the crystals of the hydrochloride salt of 1,5-diphenylbiguanide (**6a**·HCl) grown from water. The image reveals bilayers with an ionic core and a hydrophobic exterior. The view shows a 3 × 1 × 1 array of unit cells with atoms represented by spheres of van der Waals radii. Hydrogen atoms appear in white, chlorine atoms in light gray, carbon atoms in dark gray, and nitrogen atoms in black.



ture **8** appears to be a fundamental preference, both in the solid state and in solution (2).

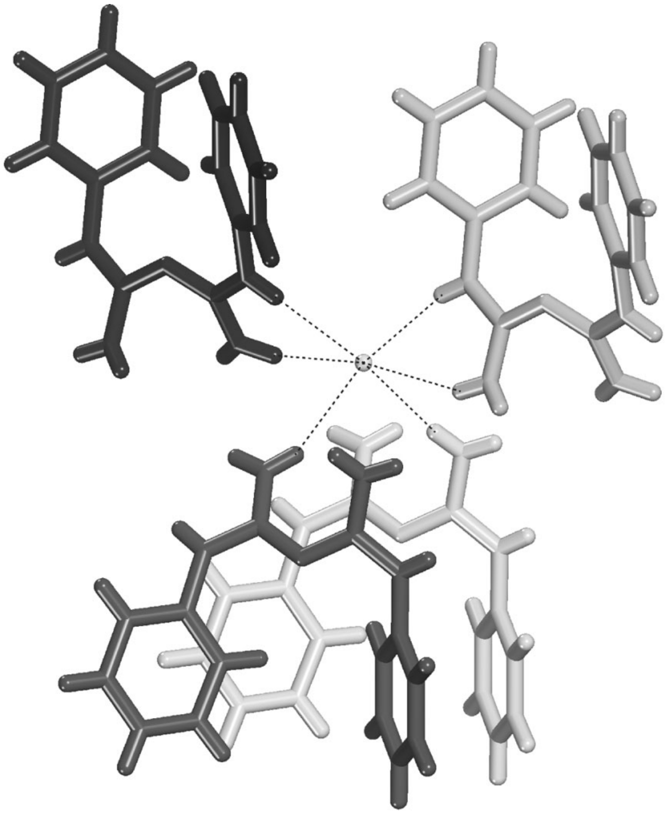
The two guanidinium subunits that can be considered to make up the biguanidinium cation lie in two distinct planes that form an angle of 22.8(4)°. The nonplanarity of the biguanidinium core presumably reduces allylic strain while permitting a significant degree of conjugation. Again, similar observations have been made in all previous structural studies of biguanidinium salts, so nonplanarity of the biguanidinium core appears to be a universal characteristic. The two phenyl rings are tilted from the guanidinium planes by angles of 52.4(1)° and 39.5(1)°, and together they form an angle of 88.8(1)°, thereby permitting an intramolecular C-H···π interaction in which the shortest C—C distance is 3.773 Å (Fig. 1). This may explain why the 1,5-diphenylbiguanidinium cation adopts the compact conformation represented by structure **11**, rather than extended conformation **12**.

The crystal structure of diphenylbiguanidinium salt **6a**·HCl is closed-packed (Fig. 2) and can be considered to consist of bilayers, with hydrophilic biguanidium cations and chloride anions occupying the core and hydrophobic phenyl groups forming the exterior.[6] The bilayers then stack along the *c* axis. Within the core of each bilayer, the principal interactions are hydrogen bonds and ionic attractions between biguanidinium and chloride. The biguanidinium ions do not interact directly with each other by forming hydrogen bonds. The absence of inter-cationic hydrogen bonds has been noted in most other biguanidinium salts (28, 29, 31, 34, 36–38), but they are nevertheless present in certain cases (25, 26, 32). Each chloride ion accepts a total of six hydrogen bonds from four neighboring biguanidinium cations (Fig. 3), two of which chelate chloride by donating two hydrogen bonds and two of which each contribute a single hydrogen bond. In turn, each biguanidinium cation forms hydrogen bonds with a total of four neighboring chloride ions, of which two are chelated and the others each accept a

---

[6] A similar bilayer organization has been noted in the structure of the monohydrochloride salt of phenformin (**13**) (32).

Fig. 3. View of the structure of the crystals of the hydrochloride salt of 1,5-diphenylbiguanide (**6a**·HCl) showing how each chloride anion is surrounded by four biguanidinium cations and accepts six ionic N-H···Cl hydrogen bonds (broken lines). Two biguanidinium cations chelate chloride and two donate single hydrogen bonds.



single hydrogen bond. Similar interactions between biguanidinium ions and halide have been observed previously (25, 28, 31, 34, 36–38). In addition, the phenyl groups of each biguanidinium cation engage in multiple aromatic contacts or interactions with phenyl groups provided by neighboring cations (Fig. 4). In total, each biguanidinium cation has four face-to-face and six edge-to-face aromatic contacts with six neighbors.

The corresponding free base (1,5-diphenylbiguanide (**6a**)) crystallized from hot ethanol in the monoclinic space group *Pc*, and one of two symmetry-independent molecules in the unit cell is shown in Fig. 5.^{5} The other molecule is closely similar and is not illustrated. Unlike the twisted biguanidinium cation, the biguanide unit has a roughly planar geometry, maintained by an intramolecular N-H···N hydrogen bond (2.06(1) Å). Similar features appear in all previous structural studies of biguanides (27, 33, 34), so a nearly planar geometry and an intramolecular hydrogen bond appear to be fundamental preferences. The C—N bond lengths within the biguanide unit range from 1.294(8) to 1.406(8) Å, suggesting significant delocalization of C—N single and double bonds, but slightly less than in the corresponding biguanidinium salt. Unlike the salt, free base **6a** favors a conformation in which no intramolecular aromatic interactions are present.

Like the corresponding biguanidinium salt, biguanide **6a** forms a closed-packed layered structure consisting of alternating hydrophobic and hydrophilic domains (Fig. 6). In the free base **6a**, however, the neutral biguanide units interact directly by hydrogen bonding. Each molecule donates two hydrogen bonds to one neighbor and accepts two hydrogen bonds from another, thereby forming a corrugated ribbon (Fig. 7). Similar intermolecular hydrogen bonding has been previously observed in the structures of biguanide (**1**) and 1-phenylbiguanide (**3**) (27, 33, 34). Curiously, the donor sites that form the shortest intermolecular hydrogen bonds are the -NH_2 groups already involved as donors in intramolecular hydrogen bonding. As expected, one of the acceptor sites is the unprotonated central nitrogen atom in each biguanide unit. The other acceptor site is the nitrogen atom of the -NH_2 group not involved in intramolecular hydrogen bonding, which forms the longest C—N bond in the biguanide unit (1.406 Å).

Individual corrugated ribbons formed by intermolecular hydrogen bonding form face-to-face aromatic interactions and stack along the *ab* diagonal to create layers (Fig. 8*a*). Stacking of the layers along the *c* axis then permits the formation of multiple C-H···π interactions (Fig. 8*b*), with the shortest C—C distances ranging from 3.600 to 3.764 Å.

Conclusions

Biguanides are an intrinsically interesting class of compounds with many known or potential applications. Despite these attractive properties, biguanides remain poorly studied. Few detailed procedures for their synthesis have been published, and full spectroscopic characterizations and structural studies are rare. As a practical guide to assist other researchers interested in using biguanides, we have summarized our experience with 1-arylbiguanides, 1,5-diarylbiguanides, and their monohydrochloride salts. Various substituted derivatives can be synthesized in good yields and high purity by simple methods based on published procedures, and these compounds can be fully characterized by standard spectroscopic methods. Structural analyses of representative compounds by X-ray diffraction confirm that arylbiguanides and their salts can form networks held together by characteristic patterns of hydrogen bonds. As a result, arylbiguanides and their salts show promise as components in supramolecular construction.

Experimental

Anilines were purified by recrystallization or distillation prior to use. All other reagents were commercial products that were used without further purification. All NMR spectra were recorded at 298 K unless noted otherwise. Mass spectra are provided only for the neutral biguanides.

1-Phenylbiguanide (3·HCl)

In a 2 L round-bottomed flask equipped with a magnetic stirrer, aniline (91.3 mL, 93.3 g, 1.00 mol) was added to aq. HCl (1 L, 1 mol/L), and the mixture was stirred until it became homogeneous. Dicyandiamide (84.1 g, 1.00 mol) was then added, and the mixture was heated at reflux with constant stirring for 12 h. The mixture was cooled to 25 °C, and

Fig. 4. View along the *c* axis of the layered structure of the crystals of the hydrochloride salt of 1,5-diphenylbiguanide (**6a**·HCl) showing multiple intermolecular aromatic interactions (broken lines) within a single layer. Hydrogen atoms appear in white, carbon atoms in gray, and nitrogen atoms in black. Each biguanidinium cation has four face-to-face and six edge-to-face aromatic contacts with six neighbors, as well as one intramolecular edge-to-face interaction (not marked by a broken line). The shortest C—C distances between phenyl rings are shown in Å.

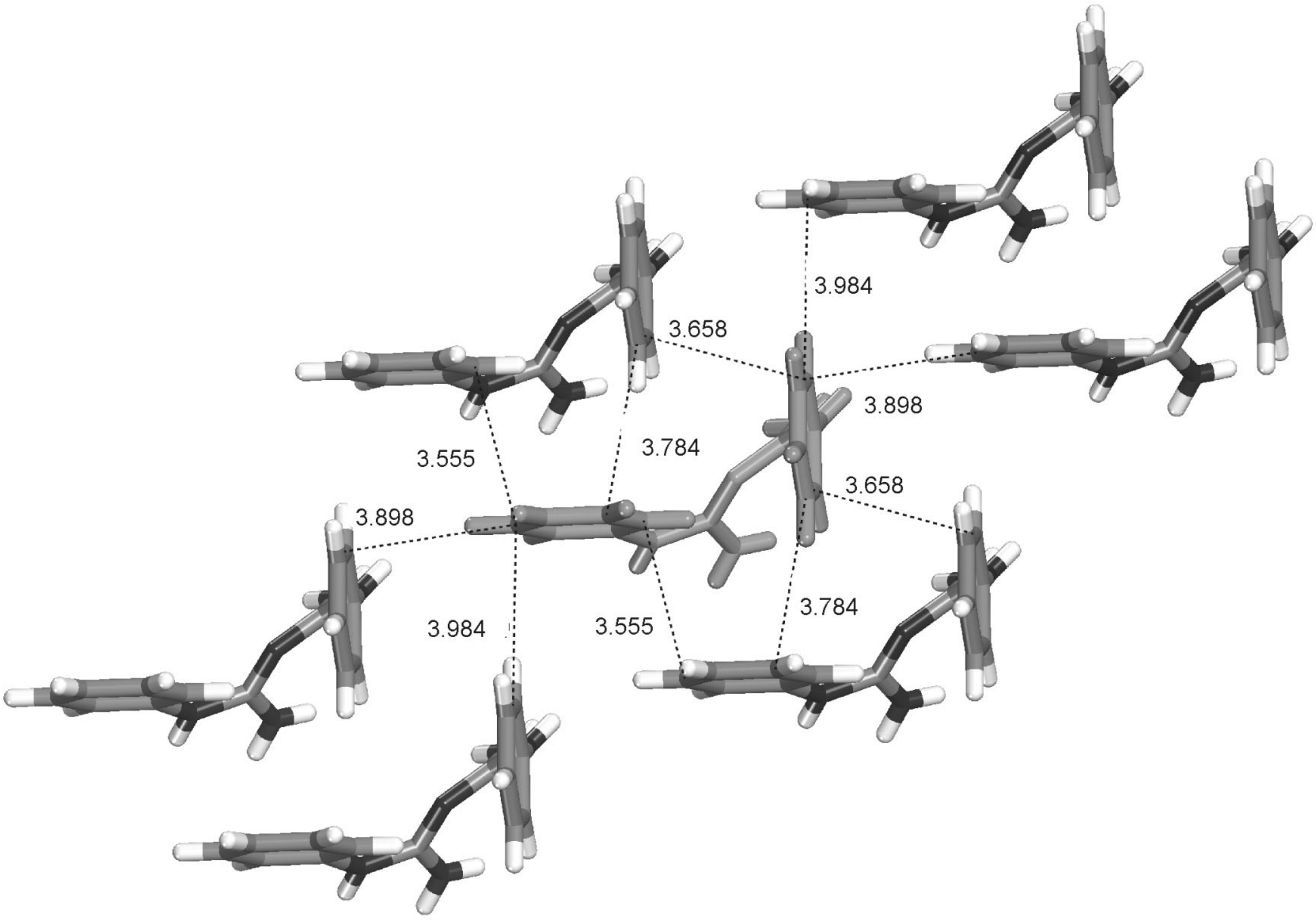
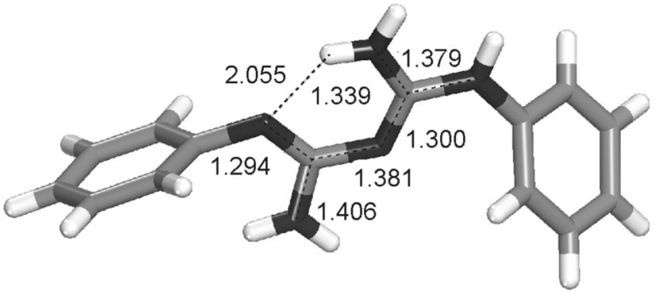


Fig. 5. View of the structure of the crystals of 1,5-diphenylbiguanide (**6a**) grown from ethanol. Hydrogen atoms appear in white, carbon atoms in gray, and nitrogen atoms in black. The intramolecular N-H···N hydrogen bond is represented by a broken line and bond lengths are shown in Å, with standard deviations provided in the Supplementary material.[5]



the resulting colorless crystals were separated by filtration and washed with THF, hexane, and acetone to yield an initial crop of 1-phenylbiguanide (**3**) monohydrochloride (159 g). Concentration of the filtrate followed by crystallization and filtration provided an additional crop of product, giving a total yield of 181 g (0.839 mol, 84%), mp 244 to 245 °C. IR (KBr, cm^{-1}): 3301 (s), 3168 (s), 1643 (s), 1604 (s), 1557 (s), 1529 (s), 1490 (s), 1455 (m), 1373 (m), 1287 (m), 1252 (w), 1075 (m). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 9.96 (s, 1H), 7.42 (s, 4H), 7.38 (d, ^{3}J = 8 Hz, 2H), 7.27 (t, ^{3}J = 8 Hz, 2H), 7.15 (s, 2H), 7.02 (t, ^{3}J = 8 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 162.1, 156.1, 139.5, 129.5, 124.1, 121.6. Anal. calcd. for $C_8H_{12}ClN_5$: C 44.97, H 5.66, N 32.78; found: C 44.84, H 5.71, N 32.58.

1-Phenylbiguanide (3)

In a 1 L round-bottomed flask equipped with a magnetic stirrer, 1-phenylbiguanide (**3**) monohydrochloride (214 g, 1.00 mol) was added to a mixture of methanol (200 mL) and methanolic $NaOCH_3$ (230 mL, 25% by weight, 1.0 mol). The resulting mixture was then stirred at 25 °C for 1 h. Suspended NaCl was separated by filtration, and solvent was removed from the filtrate by evaporation under reduced pressure. The gummy residue was triturated with hot ethanol (600 mL), and undissolved solids were removed by filtration. The filtrate was concentrated to 150 mL by partial evaporation under reduced pressure, and then hexane was

Fig. 6. View along the *a* axis of the structure of the crystals of 1,5-diphenylbiguanide (**6a**) grown from ethanol. The image reveals bilayers with a hydrophilic core and a hydrophobic exterior. The view shows a 1 × 3 × 2 array of unit cells with atoms represented by spheres of van der Waals radii. Hydrogen atoms appear in white, carbon atoms in dark gray, and nitrogen atoms in black.

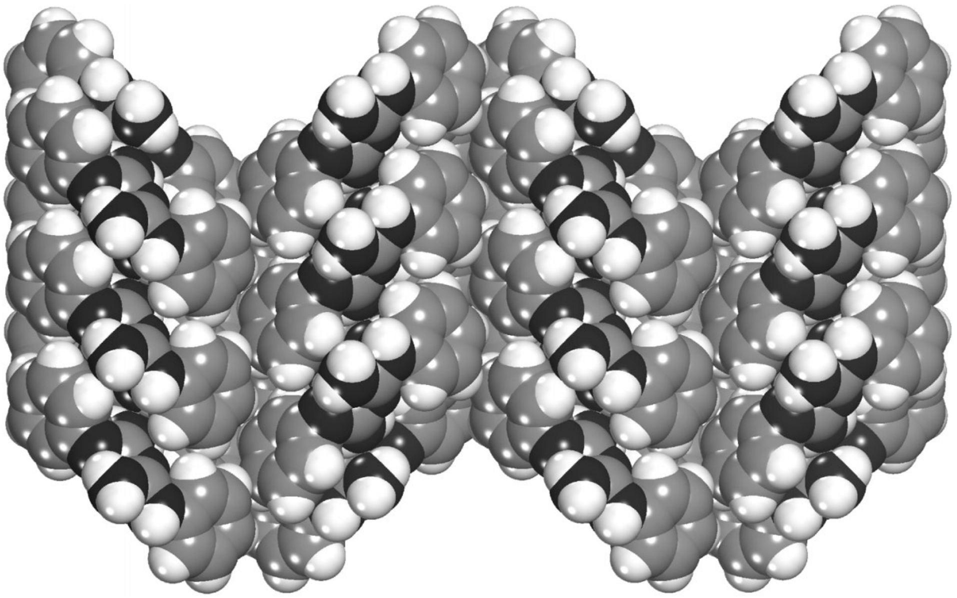
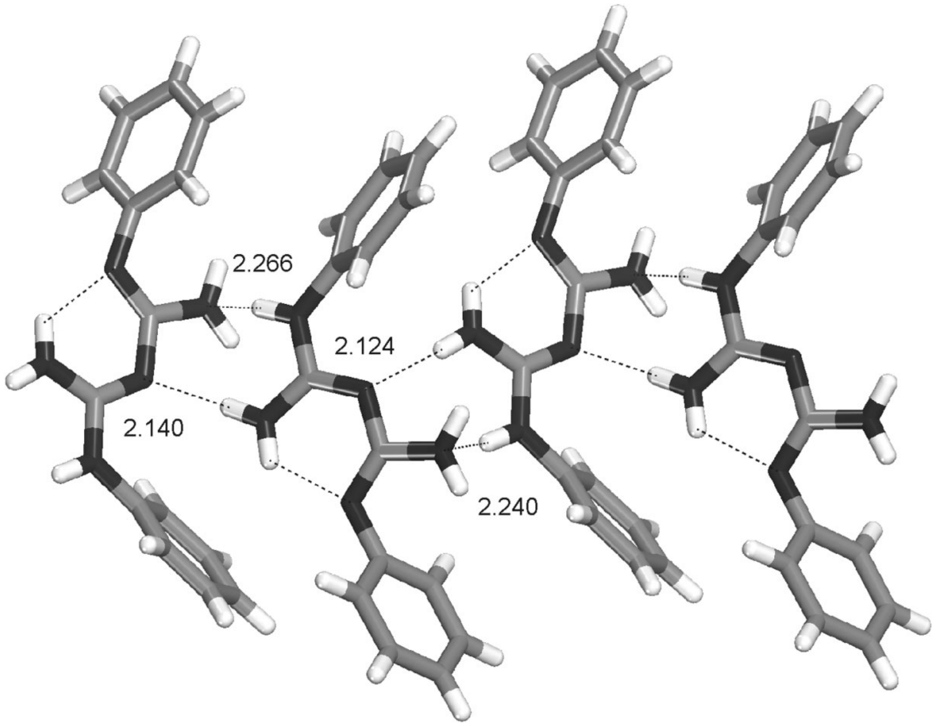
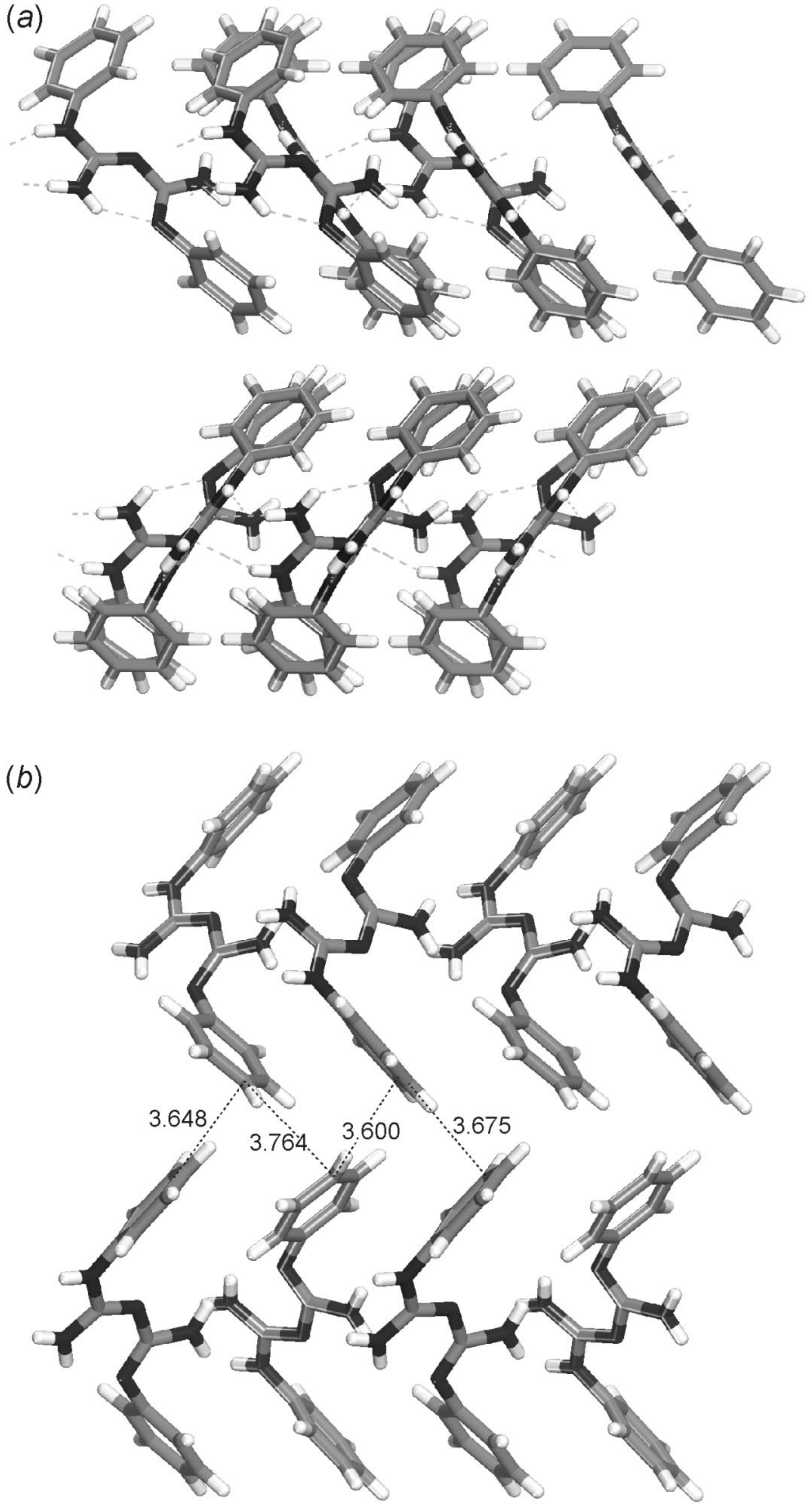


Fig. 7. View along the *ab* diagonal of the structure of 1,5-diphenylbiguanide (**6a**) showing inter- and intramolecular hydrogen bonds. The hydrogen bonds are represented by broken lines and lengths are shown in Å, with standard deviations provided in the Supplementary material.[5] Hydrogen atoms appear in white, carbon atoms in gray, and nitrogen atoms in black. Each molecule donates two hydrogen bonds to one neighbor and accepts two hydrogen bonds from another, thereby forming a corrugated ribbon.



added to precipitate the desired product, which was separated by filtration and dried under reduced pressure. This yielded pure 1-phenylbiguanide (**3**) as a colorless solid (168 g, 0.948 mol, 95%), mp 138 to 139 °C. IR (KBr, cm^{-1}): 3428 (w), 3375 (m), 3324 (m), 3153 (m), 2988 (m), 1665 (s), 1603 (s), 1555 (s), 1482 (m), 1445 (w), 1387 (m), 1363 (m), 1247 (m), 1071 (w), 756 (w), 695 (m). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.20 (t, ^{3}J = 7.6 Hz, 2H), 6.85 (t,

Fig. 8. (*a*) View along the *ab* diagonal of the structure of 1,5-diphenylbiguanide (**6a**) showing how individual corrugated ribbons formed by intermolecular hydrogen bonding (broken lines) form face-to-face aromatic interactions and stack to create layers. Hydrogen atoms appear in white, carbon atoms in gray, and nitrogen atoms in black. (*b*) View along the *b* axis, showing multiple C-H···π interactions between layers. The shortest C—C distances between phenyl rings (shown in Å) are used to define the aromatic interactions.



^3J = 7.6 Hz, 1H), 6.80 (d, ^3J = 7.6 Hz, 2H), 6.70 (bs, 4H), 4.92 (bs, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 160.2, 158.7, 151.7, 129.8, 123.7, 121.5. MAB-HR-MS (N$_2$) calcd. for $C_8H_{11}N_5$ *m/e*: 177.1014; found: 177.1022. Anal. calcd. for $C_6H_{11}N_5 \cdot 1/8H_2O$: C 53.54, H 6.32, N 39.02; found: C 53.58, H 6.30, N 39.03.

1,4-Phenylenebis(biguanide) (4·2HCl)

In a 250 mL round-bottomed flask equipped with a magnetic stirrer, 1,4-phenylenediamine (5.24 g, 48.5 mmol) was added to aq. HCl (96 mL, 1.0 mol/L, 96 mmol). Dicyandiamide (8.15 g, 96.9 mol) was then added, and the mixture was heated at reflux for 3 h. Solvent was then removed by evaporation under reduced pressure, and the residual oil was triturated with hot ethanol. The resulting solid was separated by filtration, washed with hot ethanol, and crystallized from water–acetone. The crystals were separated by filtration, washed with acetone, and dried under reduced pressure to provide pure 1,4-phenylenebis(biguanide) (**4**) dihydrochloride (10.3 g, 29.5 mmol, 61%) as a colorless solid, mp 254 to 255 °C (lit. value (39) mp 270–278 °C (dec.)). IR (KBr, cm^{-1}): 3428 (m), 3302 (s), 3186 (s), 3153 (s), 1632 (s), 1547 (s), 1497 (s), 1415 (s), 1377 (m), 1295 (w), 1240 (m), 1017 (m), 826 (m), 717 (m). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 9.74 (s, 2H), 7.26 (s, 12H), 7.04 (s, 4H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 161.8, 156.4, 135.1, 122.4. Anal. calcd. for $C_{10}H_{18}Cl_2N_{10}\cdot 1/4H_2O$: C 33.95, H 5.27, N 39.60; found: C 34.17, H 5.56, N 39.60.

1,3-Phenylenebis(biguanide) (5·2HCl)

Applied to 1,3-phenylenediamine (5.24 g, 48.5 mmol), the preceding method gave pure 1,3-phenylenebis(biguanide) (**5**) dihydrochloride (8.59 g, 24.6 mmol, 51%) as a colorless solid, mp 220 to 221 °C. IR (KBr, m^{-1}): 3313 (s), 3148 (s), 1654 (s), 1544 (s), 1454 (m), 1382 (m), 1278 (w), 1193 (w), 1083 (w), 1045 (w), 920 (w), 780 (w), 733 (w). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 9.78 (s, 2H), 7.34 (s, 8H), 7.21–7.08 (m, 4H), 7.05 (s, 4H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 162.0, 156.0, 139.8, 129.6, 116.7, 114.0. Anal. calcd. for $C_{10}H_{18}Cl_2N_{10}$: C 34.39, H 5.20; found: C 34.27, H 5.59.

1,4-Phenylenebis(biguanide) (4)

In a 100 mL round-bottomed flask equipped with a magnetic stirrer, the dihydrochloride of 1,4-phenylenebis(biguanide) (**4**, 1.05 g, 3.01 mmol) was added to a mixture of methanol (20 mL) and methanolic $NaOCH_3$ (1.6 mL, 25% by weight, 7.0 mmol). The resulting mixture was stirred at 25 °C for 1 h. The precipitate was separated by filtration, washed with cold water (10 mL) and ethanol (10 mL), and dried under reduced pressure to give pure 1,4-phenylenebis(biguanide) (**4**, 0.741 g, 2.68 mmol, 89%) as a colorless solid, mp 218 to 219 °C (lit. value (39) mp 218 to 219 °C (dec.)). IR (KBr, cm^{-1}): 3467 (m), 3434 (m), 3357 (m), 3329 (m), 3159 (m), 1641 (s), 1614 (s), 1548 (s), 1520 (s), 1493 (s), 1399 (s), 1378 (s), 1242 (s), 1090 (w), 883 (m), 840 (w), 758 (w), 722 (w). ^{1}H NMR (300 MHz, D_2O) δ: 6.86 (s, 4H). ^{13}C NMR (75 MHz, D_2O) δ: 159.8, 159.4, 142.0, 124.8. FAB-MS (3-nitrobenzyl alcohol) *m/e*: 277. FAB-HR-MS (3-nitrobenzyl alcohol) calcd. for $C_{10}H_{17}N_{10}$ *m/e*: 277.1638; found: 277.1649. Anal. calcd. for $C_{10}H_{16}N_{10}\cdot H_2O$: C 40.81, H 6.16, N 47.59; found: C 40.68, H 6.19, N 47.17.

1,3-Phenylenebis(biguanide) (5)

Applied to the dihydrochloride of 1,3-diphenylenebis(biguanide) (**5**), the preceding method gave pure 1,3-phenylenebis(biguanide) (**5**) as a colorless solid, mp 206 °C (dec.). IR (KBr, cm^{-1}): 3479 (m), 3428 (m), 3335 (m), 3109 (m), 1610 (s), 1517 (s), 1470 (s), 1369 (s), 1284 (m), 1186 (m). ^{1}H NMR (300 MHz, D_2O) δ: 7.15 (t, ^{3}J = 7.8 Hz, 1H), 6.57 (dd, ^{4}J = 2.1 Hz, ^{3}J = 7.8 Hz, 2H), 6.46 (t, ^{3}J = 2.1 Hz, 1H). ^{13}C NMR (75 MHz, D_2O) δ: 159.7, 159.1, 148.3, 130.8, 118.6, 118.3. FAB-MS (3-nitrobenzyl alcohol) *m/e*: 277, 218. TOF-HR-MS calcd. for $C_{10}H_{17}N_{10}$ *m/e*: 277.1632; found: 277.1631. Anal. calcd. for $C_{10}H_{16}N_{10}\cdot 1.5H_2O$: C 39.60, H 6.31; found: C 39.79, H 5.97.

1,5-Diphenylbiguanide (6a·HCl)

In a 250 mL round-bottomed flask equipped with a magnetic stirrer, aniline (9.31 g, 100 mmol) was added to aq. HCl (100 mL, 1 mol/L, 100 mmol). The mixture was stirred until it became homogeneous. Sodium dicyanamide (4.45 g, 50.0 mol) was then added and the mixture was heated at reflux. Within 1 h, phenyldicyandiamide (**7**, X = H) had precipitated from the mixture and heating was continued. After a total of 12 h, the mixture was cooled to 25 °C, and the precipitate was separated by filtration, washed with water, and dried under reduced pressure. The solid was dissolved in hot DMF (20 mL) and toluene (150 mL) was then added, causing the formation of a gel-like precipitate. The precipitate was separated by filtration and washed successively with toluene, hexane, and water. The product could be used without further treatment, but further purification could be achieved by crystallization from hot water, which provided the monohydrochloride of 1,5-diphenylbiguanide (**6a**, 10.1 g, 34.9 mmol, 70%) as a colorless solid, mp 230–232 °C (lit. value (41) mp 232 °C; lit. value (22) mp 220 °C). IR (KBr, cm^{-1}): 3401 (w), 3307 (m), 3181 (w), 3120 (w), 1629 (m), 1602 (m), 1577 (m), 1519 (s), 1489 (m), 1445 (m), 1382 (w), 1245 (w), 754 (w), 732 (w), 688 (w). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 9.90 (s, 2H), 7.44 (s, 4H), 7.29 (m, 8H), 7.08 (m, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 157.7, 138.8, 129.7, 125.0, 122.4. Anal. calcd. for $C_{14}H_{16}ClN_5$: C 58.03, H 5.57, N 24.17; found: C 57.94, H 5.67, N 24.20.

The monohydrochloride salts of 1,5-bis(2-methylphenyl)biguanide (**6b**), 1,5-bis(3-methylphenyl)biguanide (**6c**), 1,5-bis(4-methylphenyl)biguanide (**6d**) (41), 1,5-bis(4-methoxyphenyl)biguanide (**6e**) (41, 42), 1,5-bis(4-cyanophenyl)biguanide (**6f**), 1,5-bis(2-bromophenyl)biguanide (**6g**), 1,5-bis(4-bromophenyl)biguanide (**6h**) (42), 1,5-bis(3,5-dimethylphenyl)biguanide (**6i**), and 1,5-bis(2,4,6-trimethylphenyl)biguanide (**6j**) were prepared in the same way. Yields, melting points, spectroscopic data, and elemental analyses are provided in the Supplementary material.[5]

1,5-Diphenylbiguanide (6a)

In a 200 mL round-bottomed flask equipped with a magnetic stirrer, the monohydrochloride of 1,5-diphenylbiguanide (8.69 g, 30.0 mmol) was added to a mixture of methanol (60 mL) and methanolic $NaOCH_3$ (8.2 mL, 25% by weight, 36 mmol). The mixture was stirred at 25 °C for 1 h and then water was added. The resulting precipitate was separated by filtration, washed with water, and dried under reduced pressure to give 1,5-diphenylbiguanide (**6a**, 7.30 g, 28.8 mmol, 96%) as a colorless solid, mp 147 to 148 °C (dec.) (lit. value (41) mp 145 to 146 °C). IR (KBr, cm^{-1}): 3439 (m), 3351 (m), 3214 (m), 3071 (m), 1621 (s), 1593 (m), 1544 (s), 1522 (s), 1495 (m), 1481 (m), 1443 (m), 1380 (m), 1349 (s), 1289 (w), 1231 (s), 1155 (w), 1067 (w), 757 (m), 738 (m), 716 (m), 688 (m), 611 (m). ^{1}H NMR

(400 MHz, DMSO-d_6) δ: 7.24 (m, 8H), 6.93 (m, 2H), 9–5 (bs, 5H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 156.6, 146.0, 129.7, 122.3. FAB-MS (3-nitrobenzyl alcohol) *m/e*: 254, 237, 161, 136, 119. FAB-HR-MS (3-nitrobenzyl alcohol) calcd. for $C_{14}H_{16}N_5$: 254.1406; found: 254.1402. Anal. calcd. for $C_{14}H_{15}N_5$: C 66.38, H 5.97, N 27.65; found: C 66.41, H 6.05, N 27.80.

1,5-Bis(2-methylphenyl)biguanide (**6b**), 1,5-bis(3-methylphenyl)biguanide (**6c**), 1,5-bis(4-methylphenyl)biguanide (**6d**) (41), 1,5-bis(4-methoxyphenyl)biguanide (**6e**), 1,5-bis(4-cyanophenyl)biguanide (**6f**) (43), bis(2-bromophenyl)biguanide (**6g**), 1,5-bis(4-bromophenyl)biguanide (**6h**), 1,5-bis(3,5-dimethylphenyl)biguanide (**6i**), and 1,5-bis(2,4,6-trimethylphenyl)biguanide (**6j**) were prepared in similar yields in the same way. Yields, melting points, spectroscopic data, and elemental analyses are provided in the Supplementary material.[5]

Phenyldicyandiamide (7, X = H)

In a 100 mL round-bottomed flask equipped with a magnetic stirrer, aniline (2.45 g, 26.3 mmol) was added to aq. HCl (25 mL, 1 mol/L, 25 mmol) and the mixture was stirred until it became homogeneous. Sodium dicyanamide (2.23 g, 25.0 mmol) was then added and the mixture was heated at reflux for 2 h with constant stirring. During this period the product precipitated, and it was separated by filtration and recrystallized from CH_3CH_2OH to give pure phenyldicyandiamide (**7**, X = H; 3.49 g, 21.8 mol, 87%) as a colorless solid, mp 197 to 198 °C (lit. value (41) mp 196 to 197 °C). IR (KBr, cm^{-1}): 3407 (m), 3319 (m), 3215 (m), 3154 (m), 2973 (m), 2176 (s), 2143 (m), 1660 (m), 1608 (m), 1585 (s), 1555 (s), 1495 (s), 1449 (m), 1393 (s), 1298 (m), 1208 (m), 1065 (m), 1051 (s), 895 (w), 744 (m), 714 (m), 686 (w), 637 (w). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 9.03 (s, 1H), 7.35 (d, ^3J = 8.4 Hz, 2H), 7.30 (t, ^3J = 7.0 Hz, 2H), 7.07 (t, ^3J = 7.0 Hz, 1H), 6.98 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 160.4, 138.8, 129.7, 124.6, 122.2, 118.1. MAB-HR-MS (N_2) calcd. for $C_8H_8N_4$ *m/e*: 160.0749; found: 160.0750. Anal. calcd. for $C_8H_8N_4$: C 59.99, H 5.03, N 34.98; found: C 60.07, H 5.13, N 35.20.

X-ray crystallographic studies

The structures were solved by direct methods using SHELXS-97 (44) and refined with SHELXL-97 (45). All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined as riding atoms. They were located by a difference Fourier map for compound **6a**·HCl, whereas they were placed in ideal positions for compound **6a**.

Crystallization of compounds 6a and 6a·HCl

Single crystals of compound **6a**·HCl suitable for analysis by X-ray diffraction were grown from hot water, and crystals of free base **6a** were grown from hot ethanol.

Acknowledgments

We are grateful to the Natural Sciences and Engineering Research Council of Canada (NSERC), the Ministère de l'Éducation du Québec, the Canada Foundation for Innovation, the Canada Research Chairs Program, and Merck Frosst for financial support.

In addition, we thank Professor Jurgen Sygusch for providing access to a Bruker SMART 6000 CCD diffractometer equipped with a rotating anode.

References

1. P. Hubberstey and U. Suksangpanya. Struct. Bond. **111**, 33 (2004).
2. F. Kurzer and E.D. Pitchfork. Fortschr. Chem. Forsch. **10**, 375 (1968).
3. P. Ray. Chem. Rev. **61**, 313 (1961).
4. E. Bamberger and W. Dieckmann. Ber. **25**, 543 (1892).
5. H. Tsubouchi, K. Ohguro, K. Yasumura, H. Ishikawa, and M. Kikuchi. Bioorg. Med. Chem. Lett. **7**, 1721 (1997).
6. D. Sweeney, M.L. Raymer, and T.D. Lockwood. Biochem. Pharm. **66**, 663 (2003).
7. F.L. Rose. J. Chem. Soc. 2770 (1951).
8. R.A. Glennon, M.K. Daoud, M. Dukat, M. Teitler, K. Herrick-Davis, A. Purohit, and H. Syed. Bioorg. Med. Chem. **11**, 4449 (2003).
9. Z. Brzozowski, F. Sączewski, and M. Gdaniec. Eur. J. Med. Chem. **35**, 1053 (2000).
10. R.S. Hundal and S.E. Inzucchi. Drugs, **63**, 1879 (2003).
11. K.H. Slotta and R. Tschesche. Ber. **62B**, 1398 (1929).
12. B. Kovačević and Z.B. Maksić. Org. Lett. **3**, 1523 (2001).
13. I. Kaljurand, T. Rodima, I. Leito, I.A. Koppel, and R. Schwesinger. J. Org. Chem. **65**, 6202 (2000).
14. C.G. Overberger, F.W. Michelotti, and P.M. Carabateas. J. Am. Chem. Soc. **79**, 941 (1957).
15. D. Laliberté, T. Maris, and J.D. Wuest. J. Org. Chem. **69**, 1776 (2004).
16. J.H. Fournier, T. Maris, and J.D. Wuest. J. Org. Chem. **69**, 1762 (2004).
17. S. Mayer, D.M. Daigle, E.D. Brown, J. Khatri, and M.G. Organ. J. Comb. Chem. **6**, 776 (2004).
18. S.N. Holter and W.C. Fernelius. Inorg. Synth. **7**, 58 (1963).
19. D. Karipides and W.C. Fernelius. Inorg. Synth. **7**, 56 (1963).
20. K. Shirai and K. Sugino. J. Org. Chem. **25**, 1045 (1960).
21. S.L. Shapiro, V.A. Parrino, E. Rogow, and L. Freedman. J. Am. Chem. Soc. **81**, 3725 (1959).
22. L. Neelakantan. J. Org. Chem. **22**, 1587 (1957).
23. F.H.S. Curd and F.L. Rose. UK Patent 581 346, 1946.
24. B. Clement and U. Girreser. Magn. Reson. Chem. **37**, 662 (1999).
25. G. López-Olvera and M. Soriano-García. Anal. Sci.: X-ray Struct. Anal. [online], **20**, x151 (2004).
26. A. Martin, A.A. Pinkerton, and A. Schiemann. Acta Crystallogr. Sect. C, **C52**, 966 (1996).
27. A. Dalpiaz, V. Ferretti, P. Gilli, and V. Bertolasi. Acta Crystallogr. Sect. C, **B52**, 509 (1996).
28. M. Hariharan, S.S. Rajan, and R. Srinivasan. Acta Crystallogr. Sect. C, **C45**, 911 (1989).
29. J.M. Amigó, J.M. Martínez-Calatayud, A. Cantarero, and T. Debaerdemaeker. Acta Crystallogr. Sect. C, **C44**, 1452 (1988).
30. J.M. Amigó, J. Martínez-Calatayud, and T. Debaerdemaeker. Bull. Soc. Chim. Belg. **94**, 119 (1985).
31. C.J. Brown and L. Sengier. Acta Crystallogr. Sect. C, **C40**, 1294 (1984).
32. C. Herrnstadt, D. Mootz, and H. Wunderlich. J. Chem. Soc. Perkin Trans. 2, 735 (1979).
33. A.A. Pinkerton and D. Schwarzenbach. J. Chem. Soc. Dalton Trans. 989 (1978).
34. S.R. Ernst. Acta Crystallogr. Sect. B, **B33**, 237 (1977).
35. S.R. Ernst and F.W. Cagle, Jr. Acta Crystallogr. Sect. B, **B33**, 235 (1977).

36. R. Handa and N.N. Saha. Acta Crystallogr. Sect. B, **B29**, 554 (1973).
37. R. Handa and N.N. Saha. J. Cryst. Mol. Struct. **1**, 235 (1971).
38. C.J. Brown. J. Chem. Soc. A, 60 (1967).
39. S.R. Safir, S. Kushner, L.M. Brancone, and Y. Subbarow. J. Org. Chem. **13**, 924 (1948).
40. F.E. King, R.M. Acheson, and P.C. Spensley. J. Chem. Soc. 1366 (1948).
41. F.H.S. Curd and F.L. Rose. J. Chem. Soc. 729 (1946).
42. A.B. Sen and P.R. Singh. J. Indian Chem. Soc. **39**, 41 (1962).
43. J.N. Ashley, S.S. Berg, and R.D. MacDonald. J. Chem. Soc. 4525 (1960).
44. G.M. Sheldrick. SHELXS-97. University of Göttingen, Göttingen, Germany. 1997.
45. G.M. Sheldrick. SHELXL-97. University of Göttingen, Göttingen, Germany. 1997.